UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,180	12/12/2003	Larry Norton	93580.010100	2583

32361 7590 06/14/2007

GREENBERG TRAURIG, LLP
MET LIFE BUILDING
200 PARK AVENUE
NEW YORK, NY 10166

EXAMINER	
OLSON, ERIC	
ART UNIT	**PAPER NUMBER**
1623	

MAIL DATE	DELIVERY MODE
06/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,180	NORTON, LARRY	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-43,45-69,71-82 and 119-128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43, 45-69, 71-82, and 119-128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted April 17, 2007 wherein claims 44, 70, 83-118, and 129 are cancelled and claims 45 and 71 are amended. This application claims priority to provisional application 60/432840, filed December 12, 2002.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 17, 2007 has been entered.

Claims 40-43, 45-69, 71-82, and 119-128 are pending in this application.

Claims 40-43, 45-69, 71-82, and 119-128 as amended are examined on the merits herein.

Applicant's declaration of Larry Norton (inventor) submitted April 17, 2007, under 37 CFR 1.132, is acknowledged and will be further discussed below.

Applicant's amendment, submitted April 17, 2007, with respect to the rejection of instant claims 44, 70, 87, 97, 106, 114, and 129 under 35 USC 112, first paragraph, for

inserting new matter into the claims, has been fully considered and found to be persuasive to remove the rejection as the rejected claims are no longer pending. Therefore the rejection is withdrawn.

Applicant's amendment, submitted April 17, 2007, with respect to the rejection of instant claims 83-118 under 35 USC 112, first paragraph, for lacking enablement for a method of treating any cancer whatsoever, has been fully considered and found to be persuasive to remove the rejection as the rejected claims are no longer pending. Therefore the rejection is withdrawn.

The rejection of instant claims 40-43, 45-69, 70-86, 88-96, 98-105, 107-113, and 115-128 under 35 USC 103 as being obvious over Hudis et al. in view of Henderson et al. of record in the previous office action, is withdrawn.

The following new grounds of rejection are introduced:

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40-43, 45-69, 71-82, and 119-128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudis et. al. '99 (Reference included with PTO-1449, titled "Sequential Dose-Dense Doxorubicin, Paclitaxel, and Cyclophosphamide for Resectable High-Risk Breast Cancer :Feasibility and Efficacy", Journal of Clinical oncology (1999) Vol. 17, No. 1, pp. 93-100), in view of Henderson et al. (reference of record in previous office action) in view of Winer et al. (Reference included with PTO-1449, marked as reference B by examiner) Note that the reference Hudis et al. '99 is not the same as the reference Hudis et al. A cited in the previous office action, though it shares the same authors and appears to cite the same clinical trial of dose-dense chemotherapy. In particular, this reference was published several years after the original Hudis et al. A reference and represents the thinking of the authors at a later date.

Hudis et. al. '99 describes a course of sequential dose-dense chemotherapy using the same three drugs specified by the claimed invention. In particular, p. 95, Fig. 1 illustrates the course of treatment used, which consisted of three doses of Doxorubicin, separated by 2 weeks (14 days) each, three doses of Paclitaxel separated by 2 weeks each, and three doses of cyclophosphamide separated by 2 weeks each. The same course of treatment is described on p. 94 right column, under the heading *Treatment Plan*. Furthermore, the same paragraph mentioned above (p. 94, left column, *Treatment Plan.*) also discloses that, "All nine cycles of chemotherapy were supported by granulocyte colony stimulating factor, 5 μg/kg subcutaneously, administered on days 3 through 10." Hudis et al. '99 discusses the strategy of dose

escalation and determines that dose densification is a superior strategy to dose escalation for improving the effectiveness of chemotherapy. (p. 94, left column, paragraphs 3-4) In addition, Hudis et al. discusses the relatively high doses of the drugs used and concludes that there is no evidence that the doses used were actually superior to lower doses of 60, 600, and 175 mg/m^2 for doxorubicin, cyclophosphamide, and paclitaxel, respectively. (p. 97, paragraph 2 – p. 98, paragraph 1) Hudis et al. '99 does not teach the specific doses of 60, 175, and 600 mg/m^2 for doxorubicin, paclitaxel, and cyclophosphamide mentioned in the aforementioned claims, nor does Hudis et. al. teach the administration of said chemotherapy agents in four cycles or in an order other than doxorubicin first, paclitaxel second, and cyclophosphamide third.

Henderson et al. describes a study (CALGB 9344) comparing several chemotherapy regimens involving Doxorubicin, Paclitaxel, and Cyclophosphamide. These drugs were administered in amounts of 60, 75, and 600 mg/m^2 in four cycles each. Furthermore, the study concluded that escalation of the dose of doxorubicin produced no additional benefit.

Winer et al. discloses a study of dose intensification of paclitaxel. Doses of 175, 210, and 250 mg/m^2 were compared and it was determined that the higher doses showed no improvement in response or survival over 175 mg/m^2. Although the time to progression was longer, this benefit was offset by the greater toxicity at the higher doses.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teaching of Hudis et. al. '99 by reducing the dosage of the drugs

used and increasing the number of cycles in each treatment, as well as by administering the three drugs in the various orders disclosed in instant claims 120-125.

One of ordinary skill in the art would have been motivated to do so in order to avoid administering an excess of these toxic drugs by reducing the dose and to ensure complete eradication of cancer cells by adding a fourth cycle to each treatment, particularly in view of the teaching of Henderson et al. and Winer et al. disclosing that lower doses of these drugs are equally effective. One of ordinary skill in the art would have been motivated to administer the drugs in a different order because the neither Hudis et al. '99 nor any other prior art discloses any reason to believe that the order in which the drugs are administered in a dose-dense regimen affects the treatment outcome. In particular, because the different drugs are considered to act on different selectively sensitive sub-populations, it should not matter which sub-population is eradicated first by the chemotherapy regimen as each sub-population is only significantly affected by one particular phase of the sequential treatment.

One of ordinary skill in the art would have reasonably expected success because the reduced doses and increased number of cycles were already known to be effective for the treatment of breast cancer, and because the treatment regimen of the instant invention differs only slightly from that of Hudis et al. '99. Furthermore, determination of exact treatment regimens, including exact dosage, duration of treatment, and order of administration of various drugs, is within the ordinary skill in the practice of medicine.

Although Henderson et al. and Winer et al disclose a non-dose-dense protocol, the specific dosages used by these references can be applied to a dose-dense protocol

with a reasonable expectation of success because the differences observed between dose-dense and non-dose-dense protocols are not the result of any changes in the dose-response curve of the drugs used but rather the result of the same drug, producing the same cell kill percentage, being used more often. In fact, the theoretical rationale for dose-dense chemotherapy, disclosed on p. 93, left column, second paragraph of Hudis et al. '99, rests on the knowledge that, "In these laboratory models, anticancer drugs kill a fraction of cells (called log-kill) and this is constant regardless of the number of cells present when the drugs are administered." This statement assumes that the dose-response curve, and thus the percentage of cells killed at a given dose, does not change based on the interval between treatments. Thus the disclosure in the prior art of a particular dose of a chemotherapeutic drug used in a chemotherapy method provides a clear rationale for using the same dose in a dose-dense protocol with the expectation that the efficacy will be the same as it is in the non-dose-dense protocol.

Although Henderson et al. and Winer et al. do not examine the effect of dose escalation of cyclophosphamide on the effectiveness of these drugs, the mere fact 600 mg/m^2 was used with a reasonable measure of success by Henderson et al. provides a motivation and reasonable expectation of success for one of ordinary skill in the art to use this dose.

Furthermore, as stated by Applicant in the amendment submitted August 11, 2006, "the establishment of a dose-response curve, for a particular chemotherapeutic agent, against a particular cancer, is part of the **routine experimentation** that takes

place in the field of oncology," and, "the experimentation required to arrive at an optimal dose, for a particular chemotherapeutic agent, against a particular cancer, is **absolutely routine** in the field of oncology." Even assuming, for the sake of argument, that Hudis et al. '99 is considered on its own merits, without the additional teaching of Henderson et al., modifying the specific dosage levels disclosed by Hudis et al. '99 and discovering that the lower dosages disclosed in the instant claims are equally effective is, by Applicant's own reasoning, merely routine and ordinary experimentation which is therefore obvious over the prior art. Therefore, although Henderson et al. has been cited to demonstrate that lower doses of the disclosed chemotherapeutic agents were known in the art at the time of the invention, Henderson et al. is not necessary to repair the defect in the teaching of Hudis et al. '99 and render the instant claims obvious.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument:

Applicant's arguments submitted April 17, 2007, and the declaration submitted under 37 USC 1.132 by Larry Norton, with respect to the previous rejection of these claims in view of the Hudis et al. A reference have been fully considered as applied to the above rejection and have not been found to be persuasive to overcome the rejection of the instant claims under 35 USC 103.

Applicant asserts that the references teach away from their combination. This argument is not applicable to the later Hudis et al. 99 reference cited above as the reference specifically contrasts dose escalation with dose density, and concludes that there is no evidence that the high doses used in this study provide any additional benefit

over a dose-dense protocol using the same lower doses described by Henderson et al. It is noted that the later reference is published by the same authors and discusses the same clinical trial of dose-dense chemotherapy. Thus the conclusions of Hudis et al. '99 represent a further refinement of the conclusions of Hudis et al. A in view of further studies done in the art in the intervening period since the publication of the earlier reference and overcome any perceived "teaching away" from the claimed invention by the earlier Hudis et al. A reference.

Furthermore, the inventor argues, in the declaration under 37 CFR 1.132, submitted April 17, 2007, that under the principle of equipoise, the National Cancer Institute would not have allowed the clinical trial INT C9471 to go forward if there were a reasonable expectation that a dose-dense therapy would be superior to a non-dose-dense therapy at the given doses. This argument is not relevant to the instant case because a finding of *prima facie* obviousness does not require that the claimed invention be known to be more likely than not superior to the entirety of the prior art. According to MPEP 2145, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) Therefore it is not required that the invention be known for certain to be superior to the non-dose-dense arm of the trial. It is also noted that the decision to approve INT C9741 was made prior to the start of the study in September 1997, and therefore prior to the publication of either of the references cited in the above rejection. Therefore the

approval of INT C9741 has no bearing on whether the combination of Hudis et al. '99 and Henderson et al. (published in 1998) would lead one of ordinary skill in the art to believe that the dose-dense arm of INT C9741 would be superior to the non-dose-dense arm of this study.

Applicant also argues that the establishment of a dose-response curve and the discovery of equally-effective, lower doses to arrive at the claimed invention is not routine and ordinary experimentation because the claimed invention requires the administration of "well-tolerated" amounts of chemotherapeutic agents producing no substantial hematological side effects, and one of ordinary skill in the art would not know that the claimed amounts of chemotherapeutic agents were in fact well tolerated. However, according to MPEP 2145, "Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979)" In the instant case, motivation to combine the references is provide by the reasonable expectation that the combination would be less toxic than the therapy of Hudis et al. '99 and more effective than that of Henderson et al. The expectation of reduced toxicity is sufficient motivation to combine the references regardless of whether one skilled in the art would have known that the combination would produce no hematological toxicity at all.

Inventor's statement in the declaration under 37 CFR 1.132 filed April 17, 2007, that, "the use of an optimal amount of a chemotherapeutic agent in a sequential and/or dose dense regimen with other agents may not necessarily result in a successful clinical result due to factors such as unexpected toxicities, unexpected interactions of the

agents, and feasibility in terms of detrimental impact on the quality of life," is not considered persuasive to establish that one of ordinary skill in the art would not have had a motivation and reasonable expectation of success in combining the references, or that one of ordinary skill in the art would not have been able to determine the optimal dosage level of the different agents by ordinary and routine experimentation by modifying the higher doses taught by Hudis et al. '99 based on accepted techniques in the field of oncology. If the method disclosed by Hudis et al. '99 is an acceptable therapy, it is highly unlikely that decreasing the doses of the agents involved will produce additional unexpected toxicities, unexpected interactions of the agents, or detrimental impact on the quality of life that was not already observed for Hudis et al. '99 alone. Furthermore, it is also highly unlikely that these agents will display any unexpected interactions in a sequential dose-dense protocol that were not already observed when the agents were administered simultaneously in the same doses by Henderson et al.

Therefore, as discussed above, the declaration under 37 CFR 1.132 filed April 17, 2007 is insufficient to overcome the rejection of claims 40-43, 45-69, 71-82, and 119-128 based upon Hudis et al. '99 in view of Henderson et al. and Winer et al. as set forth in the last Office action.

For these reasons Applicant's arguments are not persuasive and the rejection is maintained.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson
Patent Examiner
AU 1623

Anna Jiang
6/7/07
Supervisory Patent Examiner
AU 1623